January 18, 2000

VETERINARY SERVICES MEMORANDUM NO. 800.200

Subject: General Licensing Considerations: Efficacy Studies

To: Biologics Licensees, Permittees, and Applicants
Directors, Center for Veterinary Biologics

I. PURPOSE

These general licensing considerations provide guidance to applicants for developing efficacy data to support an application for a U.S. Veterinary Biological Product License or U.S. Veterinary Biological Product Permit for Distribution and Sale according to 9 CFR 102.5 and 104.5.

II. CANCELLATION

This Memorandum cancels Veterinary Biologics General Licensing Considerations No. 800.200 dated May 12, 1995.

III. BACKGROUND

Licensing considerations provide guidance to applicants concerning the development of data in support of license applications and assist the Center for Veterinary Biologics-Licensing and Policy Development (CVB-LPD) in maintaining uniformity and consistency in the review of license applications. General Licensing Considerations address basic principles that have general application in the licensing of products. This document addresses the basic principles for conducting efficacy studies.

IV. GUIDELINES

A. Experimental Product

The experimental product the applicant uses for generating efficacy data must accurately represent the product that the firm will produce once a product license is granted. The applicant is responsible for establishing the validity of the experimental product used to demonstrate efficacy. The experimental product that applicants use in efficacy studies should be produced:

1. *In Accordance with the Filed Outline of Production.*

2. *In Licensed Production Facilities* - Produce the experimental product in licensed production facilities in accordance with filed facility documents and not in research facilities. (Production in research facilities is generally on a much smaller scale than commercial production, and the resulting products may have different properties.) If applicants produce the experimental product in research facilities, they should establish that this product fully represents the product that they will produce in production facilities.

3. *At or Below Minimum Potency* - The potency of the experimental product should be at or below the minimum potency provided in the Outline of Production for the product.

a. For most live virus vaccines, the titer required through dating must be at least 0.7 log greater than the titer of the product used in the efficacy study.

b. For most live bacterial vaccines, the bacterial count required through dating must be twice that of the product used in the efficacy study.

c. Killed products used in efficacy studies must be at or below the minimum antigen level specified in the Outline of Production.

4. *At the Highest Passage* - Applicants should produce the experimental product at the highest passage from the Master Seed and, if of cell culture origin, in cells at the highest passage from the Master Cell Stock allowed by the Outline of Production. Generally, the fifth passage from the Master Seed and the twentieth passage from the Master Cell Stock are the highest allowed.

B. Experimental Protocol

1. *Submission* - At least 60 days before initiating an efficacy study, the applicant should submit a protocol to the Center for Veterinary Biologics-Licensing and Policy Development (CVB-LPD) for review. The applicant should receive concurrence from CVB-LPD before beginning the study.

2. *Dates to Include* - The protocol should include the proposed dates of initiation, challenge, and conclusion of the study so that CVB personnel may arrange to observe the study at critical periods, if desired.

3. *Content of the Protocol* - The protocol should describe:

a. Specific objective(s) of the study as related to the recommended use of the product. (See section IV. C. below on efficacy data requirements.)

b. The age, breed, sex, and any other distinguishing features of animals used in the test.

c. The composition of the product, including antigenic mass, proposed potency, and how potency will be tested.

d. The composition of the placebo administered to the control group.

e. The number of subjects per treatment group. Although not required, power calculations are valuable in predicting the number of experimental subjects necessary to achieve specified objectives.

f. The method of randomly assigning treatments to subjects. This should include any stratification or blocking factors used in the experimental design, such as antibody titer, age, sex, weight, litter, or parity. While important in all efficacy studies, this is particularly critical in clinical trials involving existing conditions or relying on natural challenge.

g. The source, housing, management, and observation of subjects; methods to ensure blinding of clinical observations; and time periods during the study when different treatment groups are in contact or separated. Whenever possible, you should extend blinding to group membership as well as treatment allocations.

h. Outcomes. Define the outcomes to be measured in the study, and specify which is the primary variable and which are the secondary variables. The primary variable should provide the most clinically relevant evidence supporting the study's objective. The primary variable may be a composite of more than one clinical sign, provided an explicit case definition is stated in the protocol. Specify the criteria intended to determine whether the findings of the study indicate a satisfactory or unsatisfactory result.

i. Explicit case definitions or scoring systems. Explicit case definitions are preferable to complicated scoring systems for clinical signs. Scoring systems are best used as an aid in categorizing disease severity. Consequently, keep scoring systems as simple as possible, so that they define a distinct number of discrete categories of the outcome. Avoid incorporating quantitative outcomes,

such as body temperatures, or categorical frequencies, such as number dead, into a scoring scheme. Report them separately to avoid loss of information. Where applicable, report individual components comprising the score. Avoid analysis of composite scores as quantitative variables.

j. The methods of data analysis in sufficient detail to permit an assessment of adequacy and appropriateness. The analysis should reflect the experimental design, including the randomization scheme and the type of outcome variables measured. The analysis should include an estimate of the size of the treatment effect based on the primary outcome variable and an assessment of its clinical relevance. Accompany the estimate with an appropriate measure of its statistical precision such as a confidence interval, hypothesis test, or posterior distribution.

C. Efficacy Data Requirements

Develop data to support all label indications and recommendations for use.

1. *Label Indications* - Data must fully support label indications and accurately reflect the expected performance of the product. For example:

a. Do not use "Prevents infection with (certain microorganism)" on a label unless significant data demonstrate the product is able to prevent all colonization or replication of challenge microorganisms in vaccinated-and-challenged animals.

b. Use "For prevention of disease due to (certain microorganism)" only for those products shown to be highly effective in the prevention of clinical disease in vaccinated-and-challenged animals. That is, the entire 95% interval estimate of efficacy must be at least 80%.

c. Use claims such as "an aid in the prevention of" or "as an aid in the reduction of" for products which have demonstrated efficacy in achieving the claim. Efficacy should be estimated by the prevented fraction or other appropriate measure. The prevented fraction is the complement of the risk ratio ($1 - p_v/p_c$, where p_v is the affected fraction of vaccinates and p_c is the affected fraction of controls.)

d. When a microorganism is associated with more than one clinical form of disease, limit claims to the disease form(s) for which efficacy has been

demonstrated such as “respiratory form” or “reproductive form.” Use specific disease or syndrome names whenever applicable.

2. *Routes of Administration* - Establish efficacy for each route of administration recommended on the label (intramuscular, subcutaneous, intranasal, intraocular, in-ova, etc.).

3. *Species Recommended* - Establish efficacy in each species for which the product is recommended.

4. *Age and Susceptibility of Animals* - Conduct host animal immunogenicity studies in fully susceptible animals of the youngest age for which the product is recommended. However, if the youngest age for vaccination proposed to be recommended on product labeling is an age when interfering levels of maternal antibody may still be present:

a. Provide data to demonstrate efficacy of the product in the face of expected levels of maternal antibody, or

b. Indicate on the labeling that the product is for the vaccination of susceptible animals of the minimum age used in the immunogenicity study and recommend revaccination at appropriate intervals until such animals reach an age when interfering levels of maternal antibody would no longer be present.

5. *Onset of Immunity* - Support any specific claims concerning onset of immunity with acceptable data.

6. *Duration of Immunity* - Conduct duration of immunity studies to support vaccination recommendations for all new product fractions presented for licensure. Support any specific claims for duration of immunity for any product with acceptable data.

7. *Passive Immunity* - When recommending vaccination of adults to provide passive immunization of offspring, support label claims for passive immunity by vaccination of a significant number of adults and by challenge or other assessment of immunity in the offspring.

8. *Active and Passive Immunity* - When a product is recommended for use both in adults and in neonates for protection of neonates, use a single neonate-and-adult vaccination group with appropriate controls to demonstrate efficacy. However, if the product is also recommended for vaccination of adults alone or in neonates alone for the

protection of neonates, also demonstrate efficacy in a group where only adults are vaccinated and in a group where only neonates are vaccinated.

D. General Data Requirements

1. *Submit All Data* - Submit all data generated that relate to a product defined by a product license application to APHIS. This, for example, applies to both satisfactory and unsatisfactory results, to studies designed to select dose or antigen levels, and to definitive or repeat efficacy tests.

2. *Serological Data* - CVB-LPD generally does not accept serological data for establishing efficacy of products. CVB-LPD will only consider such data when there are reasonable data to demonstrate that the serological test used is indicative of protection. Applicants should submit protocols proposing to use serological data to establish efficacy to CVB-LPD for approval prior to initiation of such studies.

3. *Relevant Challenge Outcomes* - Data should represent clinical signs that are indicative of the disease condition under study. When using explicit case definitions or scoring systems to try to demonstrate a vaccination effect, the clinical signs in challenged animals should reflect the disease condition claimed on the label.

E. Reports

1. *Follow Protocol* - Adhere to the protocol in the execution, analysis, and report of all studies. For example, analyze the outcome criteria in the report according to the protocol. Justify and note any changes in the report.

2. *Account for All Subjects* - Account for all subjects entering the study in the report as well as in the written records.

3. *Identify Software Used* - Identify the software used in the analysis.

F. Records

1. *Location of Records* - Maintain all records generated in support of a license application on licensed premises and have these records available for inspection at all times.

2. *Recording Procedures* - Maintain legible and indelible records concurrent with each successive step in product preparation and with each stage of the experimental protocol. Identify the applicable experimental protocol in the records.

3. *Information to Record* - Include the following in the records for all prelicensing activities:

a. Initials or signature of the person responsible for the action.

b. Daily observations.

c. Identification and accountability of all product prepared, used, distributed, or returned.

d. Identification and accountability of all animals.

e. No abbreviations or acronyms unless defined.

f. Properly corrected recording errors (single line cross-out with corrected result and initials of person responsible for the correction).

g. Methods of final analysis, results, conclusions, and alternative analysis, if performed.

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